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EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1615	
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07/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,913	DITTRICH ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 04/27/09 are acknowledged.

2. Claim 12 was amended.

3. Claims 12-17 are included in the prosecution.

MAINTAINED REJECTIONS:

The following is a list of maintained rejections:

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claim 12 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Domb (US 2004/0057970 A1).

The claimed invention is a biodegradable, plastic viscous antitumor composition with prolonged release of an antitumor agent for administration into tissues, comprising: at least one antitumor agent being distributed in a carrier, consisting of biodegradable oligoester, having the numeric mean relative molecular mass M_n from 650 to 7,500, the mass mean relative molecular mass M_w from 800 to 10,000 and the glass transition temperature T_g from -35 to 45ºC, and which is prepared by polycondensation reaction of polyhydric alcohol containing at least 3 hydroxy groups with at least one aliphatic α-

hydroxy acid in the molar ratio of polyhydric alcohol to aliphatic α-hydroxy acid being from 0.5:99.5 to 12:88, wherein the essential molecule of biodegradable oligoester is a polyhydric alcohol, to the hydroxy groups of which chains created from several molecules of at least one aliphatic a-hydroxy acid are bound by ester bonds, and being in the form of homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion.

Domb teaches a "liquid polymeric implant, made of biodegradable polymer matrix loaded with an anticancer agent. The effective anticancer agent, Cisplatin or Paclitaxel, is homogeneously dispersed into the polymer matrix. The active drug is released in a controlled manner to the surrounding tissue, when placed in contact with body fluids, while the polymer carrier is eliminating itself by slow degradation. The implant in a form of ...liquid polymer... or injectable microspheres is injected into the tumor ... The implant is providing a high dose of anti-cancer drug for an extended period of time, in the tumor site, with minimal systemic drug distribution, thus, providing a localized treatment of the residual tumor cells as a complementary drug therapy to the surgery" (Page 4, [0046]).

Domb does not expressly teach the anticancer agent distributed in a biodegradable oligoester carrier prepared by a polycondensation reaction.

Hampl teaches oligoesters, specifically, a terpolymer (GA-M-DLLA) of DL-lactic acid (LA), glycolic acid (GA) and mannitol (MA), a copolymer DL-lactic acid and mannitol (M-DLLA) and lactide-glycolide copolymers (DL-PLGA) (Abstract). The GA-M-DLLA was prepared by the polycondensation reaction (Page 108, 2.2 Preparation of

oligoesters) of LA (45.05 mol), GA (45.06 mol) and MA (0.9 mol) and has a T_g of 20ºC, M_n of 2.20Kda and M_W of 3.95 kDa (Page 108, Table 1). Bovine serum albumin (BSA) was the active ingredient entrapped in microspheres prepared with the terpolymer of GA-M-DLLA which depicted prolonged release of BSA over 15 weeks (Abstract and Figures 4 and 5). The microspheres were administered subcutaneously to mice (Page 109, 2.6 Biological Experiment).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a liquid polymeric implant comprising an anticancer agent homogeneously dispersed into a biodegradable polymer matrix, as taught by Domb, substitute the polymer matrix of Domb with the terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction) that allows prolonged release of a biodegradable composition, as suggested by Hampl, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Hampl teaches that terpolymer of GA-M-DLLA allows the prolonged release of the active ingredient over 15 weeks (Abstract and Figures 4 and 5). It would have been obvious to substitute the biodegradable polymer matrix of Domb with the biodegradable polymer matrix of Domb because both matrices allow controlled release of the active ingredient.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 12, the biodegradable composition with prolonged release would have been obvious over the biodegradable composition with prolonged release taught by Hampl (Abstract and Page 108, Table 1). The limitation of the plastic viscous antitumor composition would have been obvious over the oligoester composition taught by Hampl (Abstract). This oligoester composition will intrinsically have the plastic viscous attributes as instantly claimed. The limitation of the antitumor composition and the antitumor agent would have been obvious over the antitumor composition comprising anti-cancer agents (Cisplatin and Paclitaxel) that are homogeneously distributed in the polymer matrix, as taught by Domb (Page 4, [0046]). The limitation of the "antitumor agent for administration into tissues" would have been obvious over the antitumor composition comprising Cisplatin and Paclitaxel that is injected into the tumor, as taught by Domb (Page 4, [0046]) in view of the subcutaneous administration of the composition to mice, as taught by Hampl (Page 109, 2.6 Biological Experiment). The limitation of the biodegradable oligoester would have been obvious over the terpolymer (GA-M-DLLA) taught by Hampl (Abstract). The limitation of the M_n from 650 to 7,500, the M_w from 800 to 10,000, and the T_g from -35 to 45ºC, would have been obvious over the M_n of 2.20Kda, M_W of 3.95 kDa, and T_g of 20ºC, as taught by Hampl (Page 108, Table 1). The limitation of the polycondensation reaction would have been obvious over the GA-M-DLLA that was prepared by polycondensation reaction, as taught by Hampl (Page 108, 2.2 Preparation of oligoesters). The limitation of the

polyhydric alcohol containing at least 3 hydroxy groups would have been obvious over the mannitol in the oligoester taught by Hampl (Abstract). The limitation of the aliphatic α-hydroxy acid would have been obvious over the DL-lactic acid in the oligoester taught by Hampl (Abstract). The molar ratio of the polyhydric alcohol to aliphatic α-hydroxy acid would have been obvious over the ratio of mannitol to DL-lactic acid (0.9:45.05) taught by Hampl (Page 108, Table 1). The limitation of the form of the composition as a homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion would have been obvious over the liquid polymer implant taught by Domb (Page 4, [0046]).

6. Claims 13-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Domb (US 2004/0057970 A1) and further in view of Berggren et al. (US 5,783,205).

The teachings of Hampl and Domb are stated above.

Hampl and Domb do not expressly teach a composition further comprising a liquid biocompatible plasticizer.

Berggren teaches a drug delivery device (injection) comprising an antibiotic drug and a matrix comprising a bioerodible polymer "selected from polylactic acid, polyglycolic acid, copolymers of lactic acid and glycolic acid, polylactide-co-glycerate, polyglycolide-co-glycerate and poly(orthoesters), or a bioerodible oligomer selected from oligomers of hydroxycarbonic acids and oligomers of glycolic acid and/or lactic acid and their derivatives with alcohols and/or carbonic acids" (Col. 4, lines 48-57). "The

delivery device of the invention may also optionally include an amount of a plasticizer to alter the viscosity of the matrix material so that it falls within the range required by the present invention ... Suitable biocompatible plasticizers include ... triethyl citrate, acetyl triethyl citrate ... propylene oxide ... when a plasticizer is included in the matrix material, it is generally present in an amount of from about 5 to about 30 wt %, preferably from about 7 to about 20 wt %" (Col. 9, lines 45-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a liquid polymeric implant comprising an anticancer agent homogeneously dispersed into a biodegradable polymer matrix, as taught by Domb, substitute the polymer matrix of Domb with the terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction) that allows prolonged release of a biodegradable composition, as suggested by Hampl, further combine it with the use of a plasticizer in a biodegradable and injectable composition, as taught by Berggren, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Berggren teaches that the use of a plasticizer depends on the matrix material used, for example for keeping the material from becoming too hard and brittle (Col. 9, lines 48-53) and that for altering the viscosity of the matrix material so that it falls within the range required (Col. 9, lines 45-67).

Regarding instant claims 13-14, the limitations of the one liquid biocompatible plasticizer and the plasticizer soluble in the carrier would have been obvious over the plasticizer used in the matrix material to alter the viscosity, as taught by Berggren (Col.

9, lines 45-67). One with ordinary skill in the art would know that in order to successfully alter the viscosity of the matrix material, the plasticizer used would have to be soluble in the matrix material. The limitation of the weight ratio of the plasticizer to oligoester (claim 13) would have been obvious over the ratio of triethyl citrate to PLGA, which ranges from 1:4.33 to 1:9, as shown in examples 2-5 by Berggren (Col. 13, Table B, lines 55-63).

Regarding instant claim 15, the limitation of an agent influencing the kinetics of the release of the antitumor agent would have been obvious over the "drug release-rate regulating agents" taught by Berggren (Col. 10, lines 1-2).

Regarding instant claim 16, the limitation of a stabilizer of the antitumor agent or carrier would have been obvious over the stabilizers taught by Berggren (Col. 10, lines 1-3).

Regarding instant claim 17, the limitation of heating an antitumor agent, a carrier, optionally a plasticizer, an agent influencing the kinetics of the release of the antitumor agent, and a stabilizer of the antitumor agent or a stabilizer, would have been obvious over the composition taught by Hampl (Abstract), in view of the antitumor agents taught by Domb (Page 4, [0046]), and further in view of the teaching by Berggren that the "matrix material is heated to soften the material to a point where it becomes flowable and can be delivered at a physiologically compatible elevated temperature into a biological pocket" (Col. 4, lines 14-17). One with ordinary skill in the art would heat the mixture depending on the constituents (polymer matrix, active ingredient) and depending on the administration site. The recited temperature range of 35 to 75°C

would have been an obvious variant during the process of routine experimentation, unless there is evidence of criticality or unexpected results.

Response to Arguments

Claim Objections

7. In light of Applicants' amendment of claim 12, the claim objection is withdrawn.

Rejection of claim 12 under 35 USC § 112

8. In light of Applicants' amendment of claim 12, the rejection under 35 USC § 112, first paragraph is withdrawn.

Rejection of claim 12 under 35 USC § 103(a)

9. Applicants' arguments, see Page 5, filed 04/27/09, with respect to the rejection of claim 12 under 35 USC § 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Domb (US 2004/0057970 A1) have been fully considered but are not persuasive.

Applicants argue that Hampl fails to disclose a "biodegradable oligoester" as claimed in currently amended independent claim 12 and that the oligoesters of the present invention are structurally different from Hampl's co- and terpolymers. Applicants argue that this difference is brought about by virtue of the fact that different polycondensation conditions (temperature, pressure, reaction time) are used when preparing the oligoesters of the present invention, and the conditions used when preparing the oligoesters of the present invention, allow them to reach a higher degree of branching than Hampl's co- and terpolymers.

This is not persuasive because Hampl teaches a biodegradable oligoester composition with prolonged release (Abstract and Page 108, Table 1). The limitation of the biodegradable oligoester would have been obvious over the terpolymer (GA-M-DLLA) taught by Hampl (Abstract). The limitation of the M_n from 650 to 7,500, the M_w from 800 to 10,000, and the T_g from -35 to 45ºC, would have been obvious over the M_n of 2.20Kda, M_W of 3.95 kDa, and T_g of 20ºC, as taught by Hampl (Page 108, Table 1). The limitation of the polycondensation reaction would have been obvious over the GA-M-DLLA that was prepared by polycondensation reaction, as taught by Hampl (Page 108, 2.2 Preparation of oligoesters). The limitation of the polyhydric alcohol containing at least 3 hydroxy groups would have been obvious over the mannitol in the oligoester taught by Hampl (Abstract). The limitation of the aliphatic α-hydroxy acid would have been obvious over the DL-lactic acid in the oligoester taught by Hampl (Abstract). The molar ratio of the polyhydric alcohol to aliphatic α-hydroxy acid would have been obvious over the ratio of mannitol to DL-lactic acid (0.9:45.05) taught by Hampl (Page 108, Table 1). Therefore, all the limitations of the biodegradable prolonged release oligoester composition of instant claim 12 are obviated by the teachings of Hampl. One of ordinary skill in the art would find it obvious to modify conditions (temperature, pressure, reaction time) of the polycondensation reaction based on the guidance of Hampl, during the process of routine experimentation, since these are manipulatable conditions.

It would have been obvious to one of ordinary skill in the art at the time of invention to determine all optimum and operable conditions (e.g. temperature, pressure,

reaction time), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

Applicants argue that Hampl's co- and terpolymers cannot be administered, under normal temperature and pressure conditions, in a plastic state. Applicants argue that Hampl fails to disclose a "viscous" antitumor composition as claimed in currently amended independent claim 12.

This is not persuasive because the limitation of the plastic viscous antitumor composition would have been obvious over the oligoester composition taught by Hampl (Abstract). This oligoester composition will intrinsically have the plastic viscous attributes as instantly claimed.

Applicants argue that Hampl resorts to a releasing system based on microspheres which is notoriously different from that based on the in-situ implant in form of a viscous liquid as used in the present invention. Applicants argue that the in-situ implants of the present invention are prepared in form of viscous liquid ready for instant application.

This is not persuasive because Hampl is combined with Domb and this reference teaches a liquid polymeric implant. The combination of the liquid polymeric implant with the plastic oligoester composition (with the T_g of 20°C) obviates the plastic, viscous composition as instantly claimed.

Applicants argue that the oligoesters of the present invention, have a relatively low sensitivity to changes in pH of the physiological medium into which the antitumor agent is to be released, by contrast, the polyanhydrides disclosed in Domb are known to be very sensitive to changes in pH. Applicants argue that the polyanhydrides disclosed in Domb are limited to use in brain tissue which is known as an application site having a relatively constant pH value. Applicants argue that a person of ordinary skill in the art, when trying to solve the problems addressed by the present invention would be motivated to avoid the teachings in Domb. Applicants argue that there are further differences between Domb's polyanhydrides and the oligoesters of the present invention, that ester links are considerably more resistant to hydrolysis than anhydrides, and because of the relatively low reactivity of the ester links, hydrolysis of polyesters proceeds via a homogeneous erosion throughout the whole volume of the implant. Applicants argue that by contrast, the hydrolysis of polyanhydrides proceeds on the surface of the implant since this reaction is speeder than the diffusion of water into the implant, that with polyanhydrides, the progressive degradation must precede the erosion thereof and as a result, the erosion is strongly dependent on implant geometry (size and form), and that this is not the case when using the oligoesters of the present invention.

This is not persuasive because the oligoester limitation is obviated by the teaching of Hampl (with the relative molecular mass, mean relative molecular mass, glass transition temperature). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references

individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Therefore, the rejection of 01/21/09 is maintained.

Rejection of claims 13-17 under 35 USC § 103(a)

10. Applicants' arguments, see Page 9, filed 04/27/09, with respect to the rejection of claims 13-17 under 35 USC § 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Domb (US 2004/0057970 A1) and further in view of Berggren et al. (US 5,783,205) have been fully considered but are not persuasive.

Applicants argue that as is the case with Hampl and Domb, Berggren fails to provide a teaching or suggestion which would be sufficient to motivate one of ordinary skill in the are to come up with the otherwise missing element and hence arrive at the invention claimed in currently amended independent claim 12.

This is not persuasive because the combination of Domb and Hampl obviates the limitations of claim 12. Berggren is used to remedy the deficiency of a liquid biocompatible plasticizer. The references are properly combined because Hampl teaches that terpolymer of GA-M-DLLA allows the prolonged release of the active ingredient over 15 weeks (Abstract and Figures 4 and 5). It would have been obvious to substitute the biodegradable polymer matrix of Domb with the biodegradable polymer matrix of Domb because both matrices allow controlled release of the active ingredient. One of ordinary skill in the art would have been motivated to combine Berggren with

Domb and Hampl because Berggren teaches that the use of a plasticizer depends on the matrix material used, for example for keeping the material from becoming too hard and brittle (Col. 9, lines 48-53) and that for altering the viscosity of the matrix material so that it falls within the range required (Col. 9, lines 45-67).

Therefore, the rejection of 01/21/09 is maintained.

Conclusion

11. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615